DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 19-766/S-045, S-053

Merck & Co., Inc.
Attention: Michael Elia, Ph.D.,DABT
Director, Regulatory Affairs
Sumneytown Pike, P.O. Box 4, BLA-20
West Point, PA 19486

14 NOV 2001

Dear Dr. Elia:

Please refer to your supplemental new drug applications, S-045, dated November 7, 2000, received November 8, 2000, and S-053, dated September 14, 2001, received September 17, 2001, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zocor (simvastatin) Tablets.

We acknowledge receipt of your submissions dated November 7, 2001. Your November 7, 2001, submission is a complete response to our September 25, 2001, approvable letter for S-045.

Supplement–045 provides for revisions to the **WARNINGS,** *Skeletal Muscle* subsection, **PRECAUTIONS,** and **ADVERSE REACTIONS** sections of the Package Insert.

To the **WARNINGS;** *Skeletal Muscle* subsection, the following paragraph has been added:

> "The risk of myopathy appears to be increased by concomitant administration of verapamil (see PRECAUTIONS, Drug Interactions). In an analysis of clinical trials involving 25,248 patients treated with simvastatin 20 to 80 mg, the incidence of myopathy was higher in patients receiving verapamil and simvastatin (4/635; 0.63%) than in patients taking simvastatin without a calcium channel blocker (13 patients/21,224, 0.061%)."

To the **PRECAUTIONS;** *Drug Interactions* subsection, the following sentence has been added:

> "The risk of myopathy appears to be increased by concomitant administration of verapamil."

To the **ADVERSE REACTIONS;** *Hypersensivity Reactions* subsection, "dermatomyositis" was added.

Supplement–053 provides for replacement of the previous version of the National Cholesterol Education Program (NCEP) Guidelines Table 3 with the updated NCEP Adult Treatment Panel (ATPIII) Guidelines Table 5 and an additional paragraph in the INDICATIONS AND USAGE section of the package insert.

We have completed the review of the supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the supplemental applications are approved effective on the date of this letter.

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted November 7, 2001)(copy enclosed).

Please submit the copies of final printed labeling (FPL) electronically according to the guidance for industry titled *Providing Regulatory Submissions in Electronic Format - NDA* (January 1999). Alternatively, you may submit 20 paper copies of the FPL as soon as it is available but no more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved supplements NDA 19-766/S-045, S-053." Approval of this submission by FDA is not required before the labeling is used.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, call Margaret Simoneau, R.Ph., Regulatory Project Manager, at (301) 827-6411.

Sincerely,

David G. Orloff, M.D.
Director
Division of Metabolic and Endocrine Drug Products
Office of Drug Evaluation II
Center for Drug Evaluation and Research